Controlled Stimulant Treatment of ADHD and Comorbid Tourette's Syndrome: Effects of Stimulant and Dose

F. XAVIER CASTELLANOS, M.D., JAY N. GIEDD, M.D., JOSEPHINE ELIA, M.D., WENDY L. MARSH, B.A., GAIL F. RITCHIE, M.S.W., SUSAN D. HAMBURGER, M.A., M.S., AND JUDITH L. RAPOPORT, M.D.

ABSTRACT

Objective: To determine the effects of methylphenidate (MPH) and dextroamphetamine (DEX) on tic severity in boys with attention-deficit/hyperactivity disorder (ADHD) comorbid with Tourette's syndrome. **Method:** A 9-week, placebo-controlled, double-blind crossover using a wide range of doses was completed by 20 subjects in three cohorts. **Results:** Relatively high doses of MPH and DEX in the first cohort produced significant increases in tic severity which were sustained on higher doses of DEX but which attenuated on MPH. Overall, 14 of 20 subjects continued stimulant treatment for 1 to 3 years, generally in combination with other psychotropics. Stimulant-associated adverse effects, including tic exacerbations, were reversible in all cases. **Conclusion:** A substantial minority of comorbid subjects had consistent worsening of tics on stimulants, although the majority experienced improvement in ADHD symptoms with acceptable effects on tics. MPH was better tolerated than DEX. *J. Am. Acad. Child Adolesc. Psychiatry,* 1997, 36(5):589–596. **Key Words:** methylphenidate, dextroamphetamine, tic disorders, double-blind clinical trial, attention-deficit/hyperactivity disorder.

Increased awareness of pediatric tic disorders over the past two decades was initially linked to the suggestion that stimulants used to treat attention-deficit/hyperactivity disorder (ADHD) could cause Tourette's disorder (Fras and Karlavge, 1977; Lowe et al., 1982) (historically termed Tourette's syndrome, and generally abbreviated "TS"). Although subsequent studies and clinical observations dispelled this notion (Denckla et al., 1976; Price et al., 1985), it is generally agreed that stimulants may exacerbate tics for at least some children (Cohen and Leckman, 1989; Golden, 1977, 1993), leading to continued concern about the use of stimulants in children with comorbid tic disorders. In fact, methylphenidate (MPH), though not dextroamphetamine (DEX), is labeled "contraindicated in patients who have a diagnosis or a family history of a tic disorder, including TS" in the *Physicians' Desk Reference* (Medical Economics Data, 1995).

Because ADHD symptoms are often the principal source of impairment in patients who have comorbid ADHD and TS (abbreviated TS+ADHD for convenience) (Comings and Comings, 1987; Dykens et al., 1990), alternative pharmacological treatments have been investigated (Chappell et al., 1994b; Fras and Karlavge, 1977; Hoge and Biederman, 1986; Leckman et al., 1982; Parraga et al., 1994; Riddle et al., 1988; Spencer et al., 1993a,b, 1994; Steingard et al., 1993, 1994), though rarely in controlled trials (Leckman et al., 1991; Singer et al., 1995), and still no agents rival the stimulants in short-term efficacy or in safety (Abramowicz, 1990; Gadow and Sverd, 1990; Popper and Zimnitzky, 1995; Swanson et al., 1995).

Gadow et al. (1995) examined the effect of MPH in 34 boys referred primarily for treatment of ADHD with comorbid, moderately severe tics. As expected, there were robust dose-related improvements in behavior with MPH (at doses of 0.1, 0.3, and 0.5 mg/kg

Accepted October 7, 1996.

All authors except Dr. Elia and Ms. Ritchie are with the Child Psychiatry Branch, NIMH, Bethesda, MD. Dr. Elia is currently with the Medical College of Pennsylvania, Philadelphia; Ms. Ritchie is now with the Center for Mental Health Services, Substance Abuse and Mental Health Services Administration, Rockville, MD.

The authors appreciate the assistance of NIH Clinical Center staff members including Kathy Berzin, R.N., Eddie Frazier, R.N., Catherine Heath, R.N., Jim Hoagland, R.N., and the Mental Health Outpatient Clinic Head Nurse, Susan Squires, R.N.; day program teachers Phyllis Siegrist, M.Ed., Anna Davidson, M.Ed., and Patricia Welch, M.Ed.; and recreation therapists Robin Greenfield, C.T.R.S., and Debbie Davis Cohen, C.T.R.S.

Reprint requests to Dr. Castellanos, Bldg. 10/Room 6N240, 10 Center Drive, Bethesda, MD 20892–1600.

0890-8567/97/3605–0589$03.00/0©1997 by the American Academy of Child and Adolescent Psychiatry.

b.i.d.), together with a "relatively benign," though statistically significant, dose-related increase in motor tic frequency on one measure during the 8-week treatment period, with no significant worsening on a dozen others. On the other hand, Riddle et al. (1995) observed a reduction in tic frequency in five of five subjects when MPH was temporarily discontinued after an 8- to 24-month treatment period, with increases in tic frequency in four of the five when MPH was resumed. However, this observational study was not blinded.

Our study was begun in 1990 (by J.E.) and was initially motivated by a single-blind case report of efficacy of MPH in four boys with TS+ADHD (Sverd et al., 1989). Since many children with ADHD respond preferentially to MPH or DEX (Elia et al., 1991), we included both stimulants and we used a rating scale for tics and ADHD as well as direct observation from videotapes. We now report on the first controlled study examining a wide range of doses of the two most commonly used stimulants, in boys with TS comorbid with severe ADHD. We also report on a long-term open clinical follow-up undertaken for a subset of patients in order to address the clinical effectiveness of prolonged treatment with stimulants.

METHOD

Subject Characteristics

Subjects with severe, long-standing hyperactive, inattentive, and impulsive behaviors and a diagnosis of *definite* Tourette's syndrome (as defined by the Tourette Syndrome Classification Study Group, 1993) or (for one case) *definite* chronic multiple motor tics were referred from area schools, health care providers, and the Greater Washington Chapter of the Tourette Syndrome Association over a period of 4 years to a single research social worker (G.F.R.). Subjects were required to meet *DSM-III-R* criteria for Tourette's disorder with tics confirmed by a knowledgeable clinician at least 1 year prior to referral (Tourette Syndrome Classification Study Group, 1993). Structured telephone screening was then undertaken to determine that symptoms of ADHD were present in at least two settings and that Conners hyperactivity factor scores from their home teacher were at least 2 SD greater than age norms (Werry et al., 1975). Exclusion criteria were Full Scale IQ less than 75 on the WISC-R (Wechsler, 1974), evidence of medical or neurological diseases, or any other Axis I psychiatric disorder, except obsessive-compulsive disorder, conduct or oppositional disorder, overanxious disorder, and specific developmental disorders as determined from separate interviews of the child and a parent on the Diagnostic Interview for Children and Adolescents (DICA) (Herjanic and Campbell, 1977). Approximately two dozen prospective subjects were excluded, mostly because their ADHD symptoms were not sufficiently severe. Another 16 subjects declined to participate or they embarked on their own stimulant trials while on the waiting list. Twenty-two subjects were enrolled; 20 completed the study (Table 1).

The study was approved by the National Institute of Mental Health (NIMH) Institutional Review Board and signed consent and assent were obtained from parents and subjects, respectively.

Measures

Subjects discontinued all medications for a minimum of 4 weeks, except for four children who continued to take haloperidol as described below. The final 2 to 3 weeks of medication washout took place in the NIMH Research Day Program. This period constituted the baseline evaluation, which included physical and neurological examinations, clinical and structured psychiatric interviews (DICA-P and DICA-C), laboratory tests (complete blood cell count, electrolytes, liver and thyroid panels, urinalysis, and blood lead), and a psychoeducational assessment (WISC-R and Woodcock-Johnson Achievement Battery) (Woodcock and Johnson, 1977).

The principal measures obtained during baseline and throughout the study were the Conners 39-item Teacher Rating Scale (Werry et al., 1975) completed by the day program teachers and the Historical and Examiner's Ratings from the Unified Rating Scale provided by the Tourette Syndrome Association (Kurlan et al., 1988). This scale (scores range from 0 to 104) was modified from the Yale Global Tic Severity Scale, which has demonstrated validity and reliability (Chappell et al., 1994a). Historical ratings of the variety, frequency, intensity, complexity, and interference of motor

TABLE 1
Patient Characteristics (N = 20)

	No. or Mean ± SD
Demographics	
Age (yr)	9.4 ± 2.0
Ethnicity	
Caucasion	16
African-American	2
Asian-American	1
Hispanic	1
WISC-R Full Scale IQ	98.8 ± 13.2
Verbal subscale	102.0 ± 14.6
Performance subscale	95.6 ± 11.4
Baseline ratings	
Yale Global Tic Severity Scale (0-104)	37.3 ± 14.9
Teacher 39-item Conners (0-3)	
Conduct factor	0.59 ± 0.6
Hyperactivity factor	1.98 ± 0.6
Children's Global Assessment Score (0-100)	42.60 ± 5.6
DSM-III-R diagnoses	
ADHD	20
Tourette's disorder	19
Chronic motor tics	1
Conduct disorder	1
Oppositional defiant disorder	6
Reading disorder	1
Overanxious disorder	1
Obsessive-compulsive disorder	2
Enuresis	4

Note: ADHD = attention-deficit hyperactivity disorder.

and vocal tics were derived by consensus during weekly staff meetings, based on direct observations made that week by day program teachers, recreation therapists, and psychiatric nurses. Examiner ratings of motor and vocal tic variety, intensity, complexity, interference, and distribution were obtained from videotaped recordings made through an observation mirror while subjects were in the classroom. Videotapes were recorded approximately 2.5 hours after morning medications; the first 5 minutes of each weekly tape was rated. Weekly segments were coded so that the rater was blind to drug phase and dose. Five of 200 videotapes were unavailable and group cell means were substituted. Interrater reliability for 10 randomly selected tapes was good (intraclass correlation coefficient = .88, $p < .0001$).

Design of the Controlled Trial

After the baseline period, subjects participated in a 9-week double-blind, placebo-controlled crossover trial of MPH and DEX described elsewhere in more detail (Borcherding et al., 1989; Elia et al., 1991). Briefly, subjects were randomly assigned to a crossover trial of 3 weeks each of MPH, DEX, or placebo. Doses were given twice daily at breakfast and lunch in identical capsules prepared by the NIH Pharmacy.

The main study group consisted of 12 boys between the ages of 6 and 13 years, of whom 10 completed the protocol. These subjects all underwent weekly increases in their stimulant dose (termed "low-medium-high"). For body weight of more than 30 kg, weekly MPH doses were 15, 25, and 45 mg/dose b.i.d. (for weight 30 kg or less, 12.5, 20, and 35 mg b.i.d.). Means (SD) were 0.43 (0.09), 0.67 (0.1), and 1.20 (0.17) mg/kg per dose. Weekly DEX doses were 7.5, 15, and 22.5 mg/dose b.i.d. (for weight 30 kg or less, 5, 12.5, and 20 mg b.i.d.). Means were 0.20 (0.05), 0.41 (0.07), and 0.64 (0.12) mg/kg b.i.d. These doses were being used contemporaneously in another study of boys with ADHD who were believed to be possible nonresponders to stimulants (Elia et al., 1991). They were also chosen for this study because of a case report that suggested that tic severity might be lower on higher doses of MPH (Sverd et al., 1989). Three of the patients in this first cohort received a constant dose of haloperidol throughout the study (mean dose 1.5 [0.5] mg/day, range 1 to 2).

Because of the substantial doses used, dose and order effects were confounded for this first group. To further explore the findings of this experiment, two other small groups were added. First, 6 boys between ages of 7 and 12 were added, all of whom completed the protocol. These subjects underwent the same dose increase from the first to the second week for each stimulant, but then continued to take that same dose for a third week ("low-medium-medium"). Average doses were 0.42 (0.03) and 0.69 (0.05) mg/kg for MPH and 0.19 (0.03) and 0.41 (0.03) mg/kg per dose for DEX. One subject took haloperidol (0.5 mg/day) throughout the study.

Finally, four boys between the ages of 8 and 9 years were treated with a stimulant dose increasing from a mean of 0.45 (0.07) to 1.22 (0.19) mg/kg per dose MPH from week 1 to week 2 and sustained at that same dose for a third week ("low-high-high"). Average DEX doses were 0.19 (0.01) and 0.66 (0.13) mg/kg per dose. These subjects did not take any other medications during the trial.

At the conclusion of each subject's double-blind trial, the discharge medication was chosen by team consensus before breaking the medication code.

Open Clinical Follow-up

Thirteen of the first 16 subjects (groups 1 and 2) were prescribed a stimulant at discharge, and open clinical follow-up was conducted on a monthly basis for an average of 22 months (range 6 to 36 months) using the same measures for rating motor and vocal tics used during the controlled trial. Historical ratings were provided by the child and a parent, and Examiner's Ratings were determined by the same child psychiatrist (F.X.C.). Medications were adjusted as clinically appropriate by the same physician in all but one case.

Statistical Analysis

The primary dependent measures were weekly ratings of tic severity consisting of the sum of the Historical and Examiner's Ratings from the Tourette Syndrome Unified Rating Scale and Conners teachers' hyperactivity ratings. Repeated-measures analyses of variance with drug (placebo, MPH, DEX) and week (1, 2, or 3) as the within-subject factors were performed for each cohort using SAS version 6.07 with the Greenhouse-Geyser correction for multiple comparisons. Bonferroni post hoc t tests were applied to significant main effects and interactions to determine whether preplanned pairwise comparisons were significant at $\alpha = .05$. Comparisons between MPH and DEX were performed by combining all subjects during week 1 for the low dose, groups 1 and 2 during week 2 for the medium dose, and groups 1 and 3 during week 3 for the high dose.

RESULTS

Ten out of 12 patients in the first group completed the protocol. One patient had a severe exacerbation of tics during the first blinded phase (placebo) and was dropped from the protocol. A second patient was withdrawn at his parents' request when his behavior became excessively disruptive on the low dose of DEX. Their data are not included in subsequent analyses.

Analysis of variance of total tic severity scores showed a significant interaction between drug and dose ($F = 3.50$ [4,36], $p = .03$). As is shown in Figure 1, tic severity was significantly greater (by Bonferroni post hoc t tests) during the second and third weeks of DEX and during the second week of MPH ($p < .01$) than during any of the placebo weeks, or during the third week of MPH. As expected, both stimulants significantly decreased hyperactivity as measured by day program teachers ($F = 10.4$ [2,18], $p = .001$), although there was no significant interaction between drug and dose indicating that additional improvements in hyperactivity were not observed for higher doses.

To partially deconfound the possible effects of stimulant dose from duration of stimulant treatment, six new subjects were given the same intermediate dose of each stimulant for the last 2 weeks of each drug

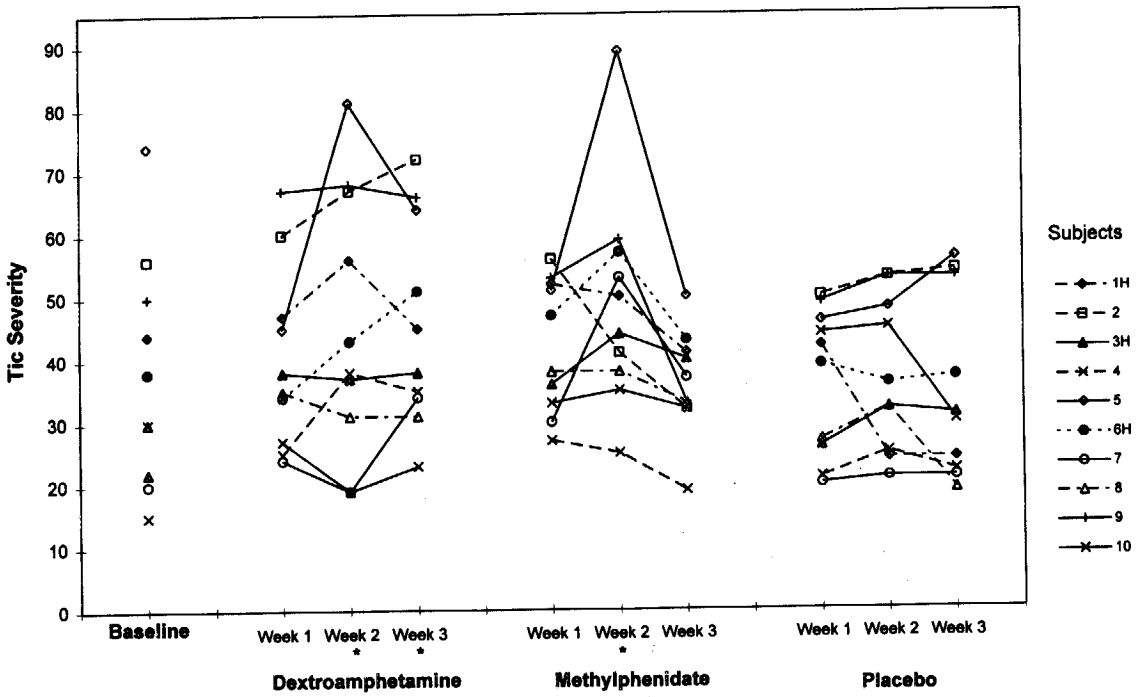

Fig. 1 Yale Global Tic Severity Scale scores for 10 boys with Tourette's syndrome and attention-deficit/hyperactivity disorder during baseline evaluation and double-blind treatment with increasing doses ("low-medium-high"; see text) of dextroamphetamine, methylphenidate, and placebo. *Mean significantly different from placebo, $p < .05$. H = constant dose of haloperidol.

phase ("low-medium-medium"). Although hyperactivity ratings were, as expected, significantly decreased by stimulants compared with placebo (F = 8.50 [2,10], p = .03), there was not a significant main effect of drug on tic severity (F = 0.89 [2,18], not significant [NS]). The drug by duration interaction did not reach significance (F = 2.06 [4,36], p = .13) for this smaller cohort, although tic severity was less severe during the third week of MPH than during the first week for four of six subjects; the same pattern was observed for three of six subjects on DEX.

An additional four subjects were recruited to test the possibility that maximal MPH dose was required to consistently produce the curvilinear dose response detected in the first cohort. This third cohort began with 1 week on "low dose" stimulant (mean 0.45 mg/kg per dose MPH, 0.19 mg/kg per dose DEX), and then was given a high dose for weeks 2 and 3 (mean 1.22 mg/kg per dose MPH, 0.66 mg/kg per dose DEX). Hyperactivity was significantly decreased by both stimulants (drug F = 11.46 [2,6], p = .03). There was a statistical trend for tic severity to be greater on DEX, although this effect did not reach significance (F = 4.78 [2,6], p = .11). The interaction of drug and dose was also not statistically significant (F = 0.60 [4,12], NS).

Comparisons Between Methylphenidate and Dextroamphetamine

When ratings on the lowest dose were compared across the entire subject group (n = 20), there was no significant effect of either stimulant on tic severity rating (F = 1.36 [2,38], p = .27). When the data from subjects who received medium stimulant doses were combined (second week for groups 1 and 2, n = 16), the overall effect of drug was again not significant (F = 1.97 [2,30], p = .16), although MPH produced tic severity ratings that were 21% greater than placebo (p = .08). When the data from subjects who received high doses were combined (third week ratings for groups 1 and 3, n = 14), the overall effect of drug was significant (F = 5.97 [2,26], p = .01). Post hoc Bonferroni t tests showed DEX resulted in significantly greater tic severity (+25%) than placebo ($p < .05$), while tic severity on MPH was indistinguishable from placebo (−4%).

Adverse Effects

Adverse effects (Guy, 1976) included marked appetite suppression with transient weight loss (n = 3 on MPH, 4 on DEX), initial insomnia (n = 2 on MPH, 10 on DEX, 1 on placebo), all of which remitted with change of medication or decrease in dose. Largely transient obsessive-compulsive symptoms were also noted (n = 5 on MPH, 1 on DEX) including retracing letters, excessive erasing, rearranging and collecting compulsions, and obsessional sexual thoughts. One of the four subjects in the "low-high-high" cohort was unable to complete the final week of high-dose DEX because of vomiting, which subsided when the medication was discontinued. As noted previously, the only subject who had such a severe exacerbation of his tics that he had to discontinue the study was taking placebo. The subject who met criteria for overanxious disorder (subject 10 in Fig. 1) experienced increased tic severity and mildly increased anxiety relative to baseline during both double-blind medication phases which abated by the third week of placebo (his last phase).

Discharge Medications

Of the 20 subjects completing the protocol, 3 subjects had greater tic severity scores on all doses of both stimulants than at baseline, and they discontinued stimulant treatment at the completion of the double-blind trial. A stimulant was prescribed for 17 subjects at the time of discharge (11 MPH, 6 DEX) (p = NS).

Open Clinical Follow-up

Thirteen subjects from groups 1 and 2 who had been prescribed a stimulant at discharge were followed monthly for an average of 22 months (range 6 to 36 months) to determine the long-term effectiveness of stimulant treatment in comorbid patients. Stimulant doses were adjusted to minimize adverse effects, and combined pharmacotherapy was instituted to minimize comorbid symptoms and to moderate tic severity.

Of eight subjects who were prescribed MPH at discharge (mean dose 47 mg/day, range 20 to 70 mg), only two continued with monotherapy throughout follow-up. Four children received one other psychotropic medication (two received clonidine, and one imipramine throughout follow-up; one received haloperidol for 6 months). One child received adjunctive clomipramine and lorazepam for obsessive-compulsive disorder. Another subject continued haloperidol from the double-blind phase (1.5 mg/day), to which clomipramine was added for obsessive-compulsive symptoms.

Six of the eight children followed on long-term MPH maintained tic severity scores consistently below their stimulant-free baseline. In all cases, clinical doses used for long-term follow-up were lower than the maximal doses tested during the double-blind trial.

Of the five children who were discharged on DEX and followed prospectively, only one had tic ratings during the follow-up interval that remained consistently below his initial baseline. This child (subject 1) had continued haloperidol treatment throughout the double-blind phase and was able to discontinue it during follow-up. Another subject continued to have moderately severe tics on DEX (which were less severe during medication holidays) but was unable to function in a special school without it. Haloperidol (1 mg/day), begun after the double-blind trial, was moderately beneficial for 16 months and was discontinued for the final 12 months of follow-up. Another subject continued to take haloperidol throughout the follow-up interval with doses up to 4 mg/day. He was treated in an inpatient facility and in residential treatment with a variety of other agents, along with DEX.

At the time of manuscript preparation, a final follow-up was conducted by telephone with 21 of the 22 enrolled subjects to determine medication status 1 to 4 years after study entry. Besides the three subjects who had experienced consistent worsening of their tics during the double-blind study, three additional subjects eventually discontinued stimulants because of deleterious effects on tics. One was treated with DEX for 6 months and also tried MPH with and without clonidine. The other received MPH monotherapy for 2 years and had several tic exacerbations which were temporally associated with streptococcal infections as documented in a case report (Allen et al., 1995). No additional information was available for the third. Ironically, the child who experienced severe worsening of tics on double-blind placebo had minimal tics on open MPH and DEX. He continued on open MPH monotherapy (40 mg/day) for 4 years with an excellent clinical response. Thus of the 22 subjects who entered this study, 15 continued to derive sufficient benefit from stimulant treatment to warrant continuing it on a long-term basis.

DISCUSSION

Double-Blind Phase

This is the first controlled comparison of MPH and DEX in boys with severe ADHD comorbid with TS. We found that our "low doses" (approximately 15 mg b.i.d. for MPH) did not significantly increase tic severity, but that relatively high doses of MPH and DEX did result in significant increases in tic severity. Interestingly, tic severity increases returned to placebo levels when MPH was sustained or increased (for 17 of 20), but only 9 of 20 displayed such a decrease from week 1 to week 3 on DEX ($\chi^2 = 7.03$, $df = 1$, $p < .01$). Among the 14 subjects who received high doses, tic severity was significantly greater on DEX than on MPH or placebo. Such differences in tic severity were reflected in the selection of MPH as the discharge stimulant for 11 (65%) of 17 patients. Although this latter difference was not statistically significant, it is worth noting, since MPH is the only stimulant listed as contraindicated for TS patients (Medical Economics Data, 1995).

Tic disorders are known to "wax and wane" and our tic ratings were highly variable even during placebo, as is shown in Figure 1. Such variability can obscure drug effects, especially with small sample sizes. Among our subjects, there were some who had marked increases in their tics associated with stimulants (such as subject 10 in Fig. 1), and there were others whose tics improved on stimulants. Tic exacerbations associated with increases of medication diminished within several days to 2 weeks after a medication phase change. The most severe exacerbation, which included self-injurious behavior, took place on double-blind placebo and resolved within a week of single-blind placebo treatment. This patient went on to do well on long-term MPH monotherapy.

Open Follow-up

Our long-term open follow-up allowed us to study the effectiveness of these stimulants, although in lower doses than during the controlled trials, because of adverse effects on appetite and sleep. Our results support an advantage for MPH, as six of eight subjects showed decreased tics and only one continued to require adjunctive haloperidol. In contrast, of five subjects taking DEX at discharge, only one had an excellent long-term course. Another stopped all medications after unsuccessful trials with both stimulants. The other three continued to take DEX because of its benefits for their ADHD, but their monthly tic ratings generally remained above their baseline scores.

During follow-up, most patients were treated with adjunctive pharmacotherapy (Wilens et al., 1995). Clonidine or haloperidol was used to attenuate tics, clomipramine was used for comorbid obsessive-compulsive disorder, and imipramine for synergistic treatment of ADHD and tics (Singer et al., 1995; Spencer et al., 1993b, 1994). Despite such approaches, a substantial proportion of our small sample (one third) continued to have stimulant-associated exacerbations of their tic disorder which outweighed the clinical benefits of the stimulants.

Naturalistic follow-up continued to show fluctuations in tic severity independent of changes in medications. It is notable, however, that summer and other briefer drug holidays produced consistent improvements in tic severity even in subjects whose tics were mild while taking stimulants. This was recorded objectively during a psychophysiological experiment with a subset of eight subjects in which tics were counted during pre- and poststimulant sessions (Andrews et al., 1994). Significant increases in tic frequency were detected poststimulant, confirming the observations of Riddle et al. (1995).

Limitations

The conclusions of this study are limited by several factors besides small sample size. For clinical and ethical reasons, drug dosage was not randomized, leaving questions of dosage and duration of drug exposure confounded. For ethical reasons, we allowed four subjects to continue on a constant dose of haloperidol, although this did not appear to affect our results (three are shown in Fig. 1 with filled symbols). The exploration of different dose schedules (cohorts 2 and 3) was limited, greatly weakening statistical power. Tic ratings were done using portions taken from the 1988 version of the Unified Tourette Syndrome Rating Scale, which has since been psychometrically updated. Finally, since MPH undergoes much more rapid and complete metabolism than DEX (Faraj et al., 1974; Greenhill, 1992), we would expect the blood level curves of the two stimulants to differ markedly. However, we did not obtain pharmacokinetic measures, so we cannot determine whether the differences in tic severity

between the two stimulants were the result of pharmacokinetic or pharmacodynamic differences. Pharmacokinetic measures might be profitably studied in future investigations of comorbid ADHD and tics.

Conclusion

At the lowest doses used in this study (which correspond to the highest doses tested by Gadow et al., 1995), we confirmed that stimulants did not produce statistically significant effects on ratings of tic severity, because tic severity worsened for some patients and improved for others while target behaviors in the classroom improved for all. At higher doses, tic exacerbations became more common, although this was often temporary on MPH. The clinical implication of these two studies is that stimulants, and in particular MPH, should be considered as therapeutic options for children with ADHD and TS, although children and their parents should be advised that the scientific basis for these decisions remains scant. Consistent with sound clinical practice, the lowest effective stimulant doses should be used, as these were the least likely to produce significant increases in tic severity and there was no evidence of significantly increased improvement in ratings of ADHD symptoms with higher doses. The tendency of MPH-associated tic exacerbations to diminish over time suggests that slower increases than usual may produce optimal improvements in ADHD symptoms with minimal worsening of TS. Finally, there may be a role for adjunctive treatments, such as α_1 agonists in the treatment of comorbid patients, although this was not systematically assessed in this study. Fortunately, the National Institute of Neurologic Disorders and Stroke has just funded a large multisite collaborative study of the effects of MPH and clonidine in ADHD+TS (personal communication, Dr. Peter Como, August 1996). Results from this placebo-controlled, two-by-two factorial design will address many of the questions left unanswered by the present study.

REFERENCES

Abramowicz M (1990), Sudden death in children treated with a tricyclic antidepressant. *Med Lett Drugs Ther* 32:53

Allen AJ, Leonard HL, Swedo SE (1995), Case study: a new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry* 34:307–311

Andrews R, Greenberg BD, Castellanos FX (1994), Startle modulation in boys with Tourette's and attention deficit hyperactivity disorder. In: *Scientific Proceedings of the Annual Meeting, American Academy of Child and Adolescent Psychiatry* 10:74 (abstract)

Borcherding BG, Keysor CS, Cooper TB, Rapoport JL (1989), Differential effects of methylphenidate and dextroamphetamine on the motor activity level of hyperactive children. *Neuropsychopharmacology* 2:255–263

Chappell PB, McSwiggan-Hardin MT, Scahill L et al. (1994a), Videotape tic counts in the assessment of Tourette's syndrome: stability, reliability, and validity. *J Am Acad Child Adolesc Psychiatry* 33:386–393

Chappell PB, Riddle MA, Scahill L, Schultz R, Leckman JF, Cohen DJ (1994b), Guanfacine treatment of children with ADHD and tics: preliminary experience. *Scientific Proceedings of the Annual Meeting, American Academy of Child and Adolescent Psychiatry* 10:48 (abstract)

Cohen DJ, Leckman JF (1989), Commentary on "Methylphenidate treatment of attention-deficit hyperactivity disorder in boys with Tourette's syndrome." *J Am Acad Child Adolesc Psychiatry* 28:580–582

Comings DE, Comings BG (1987), A controlled study of Tourette syndrome. I. Attention deficit disorder, learning disorders, and school problems. *Am J Hum Genet* 41:701–741

Denckla MB, Bemporad JR, MacKay MC (1976), Tics following methylphenidate administration. A report of 20 cases. *JAMA* 235:1349–1351

Dykens E, Leckman JF, Riddle M, Hardin M, Schwartz S, Cohen D (1990), Intellectual, academic, and adaptive functioning of Tourette syndrome children with and without attention deficit disorder. *J Abnorm Child Psychol* 18:607–615

Elia J, Borcherding BG, Rapoport JL, Keysor CS (1991), Methylphenidate and dextroamphetamine treatments of hyperactivity: are there true nonresponders? *Psychiatry Res* 36:141–155

Faraj BA, Israili ZH, Perel JM et al. (1974), Metabolism and disposition of methylphenidate-14C: studies in man and animals. *J Pharmacol Exp Ther* 191:535–547

Fras I, Karlavge J (1977), The use of methylphenidate and imipramine in Gilles de la Tourette's disease in children. *Am J Psychiatry* 134:195–197

Gadow KD, Sverd J (1990), Stimulants for ADHD in child patients with Tourette's syndrome: the issue of relative risk. *J Dev Behav Pediatr* 11:269–271

Gadow KD, Sverd J, Nolan EE, Sprafkin J (1995), Efficacy of methylphenidate for ADHD in children with tic disorder. *Arch Gen Psychiatry* 52:444–455

Golden GS (1977), The effect of central nervous system stimulants on Tourette syndrome. *Ann Neurol* 2:69–70

Golden GS (1993), Treatment of attention deficit hyperactivity disorder. In: *Handbook of Tourette's Syndrome and Related Tic and Behavioral Disorders*, Kurlan R, ed. New York: Marcel Dekker, pp 423–430

Greenhill LL (1992), Pharmacologic treatment of attention deficit hyperactivity disorder. *Child Adolesc Psychiatr Clin North Am* 1:411–447

Guy W (1976), Subject's Treatment Emergent Symptom Scale. In: *Assessment Manual for Psychopharmacology*, Guy W, ed. Washington, DC: US Government Printing Office, pp 347–350

Herjanic B, Campbell W (1977), Differentiating psychiatrically disturbed children on the basis of a structured interview. *J Abnorm Child Psychol* 5:127–134

Hoge SK, Biederman J (1986), A case of Tourette's syndrome with symptoms of attention deficit disorder treated with desipramine. *J Clin Psychiatry* 47:478–479

Kurlan R, Riddle M, Como P (1988), *Tourette Syndrome Unified Rating Scale.* Bayside, NY: Tourette Syndrome Association

Leckman JF, Cohen DJ, Detlor J et al. (1982), Clonidine in the treatment of Tourette's syndrome: a review of data. In: *Gilles de la Tourette Syndrome*, Friedhoff AJ, Chase TN, eds. New York: Raven Press, pp 391–401

Leckman JF, Hardin MT, Riddle MA, Stevenson J, Ort SI, Cohen DJ (1991), Clonidine treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 48:324–328

Lowe TL, Cohen DJ, Detlor J, Kremenitzer MW, Shaywitz BA (1982), Stimulant medications precipitate Tourette's syndrome. *JAMA* 247:1729–1731

Medical Economics Data (1995), *Physicians' Desk Reference.* Montvale, NJ: Medical Economics Company

Parraga HC, Kelly DP, Parraga MI, Cochran MK, Maxim LT (1994), Combined psychostimulant and tricyclic antidepressant treatment of

Tourette's syndrome and comorbid disorders in children. *J Child Adolesc Psychopharmacol* 4:113–122

Popper CW, Zimnitzky B (1995), Sudden death putatively related to desipramine treatment in youth: a fifth case and a review of speculative mechanisms. *J Child Adolesc Psychopharmacol* 5:283–300

Price RA, Kidd KK, Cohen DJ, Pauls DL, Leckman JF (1985), A twin study of Tourette syndrome. *Arch Gen Psychiatry* 42:815–820

Riddle MA, Hardin MT, Cho SC, Woolston JL, Leckman JF (1988), Desipramine treatment of boys with attention-deficit hyperactivity disorder and tics: preliminary clinical experience. *J Am Acad Child Adolesc Psychiatry* 27:811–814

Riddle MA, Lynch KA, Scahill L, deVries A, Cohen DJ, Leckman JF (1995), Methylphenidate discontinuation and reinitiation during long-term treatment of children with Tourette's disorder and attention-deficit hyperactivity disorder: a pilot study. *J Child Adolesc Psychopharmacol* 5:205–214

Singer HS, Brown J, Quaskey S, Rosenberg LA, Mellits ED, Denckla MB (1995), The treatment of attention-deficit hyperactivity disorder in Tourette's syndrome: a double-blind placebo-controlled study with clonidine and desipramine. *Pediatrics* 95:74–81

Spencer T, Biederman J, Steingard R, Wilens T (1993a), Bupropion exacerbates tics in children with attention-deficit hyperactivity disorder and Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry* 32:211–214

Spencer T, Biederman J, Wilens T (1994), Tricyclic antidepressant treatment of children with ADHD and tic disorders. *J Am Acad Child Adolesc Psychiatry* 33:1203–1204

Spencer T, Biederman J, Wilens T, Steingard R, Geist D (1993b), Nortriptyline treatment of children with attention-deficit hyperactivity disorder and tic disorder or Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry* 32:205–210

Steingard R, Biederman J, Spencer T, Wilens T, Gonzalez A (1993), Comparison of clonidine response in the treatment of attention-deficit hyperactivity disorder with and without comorbid tic disorders. *J Am Acad Child Adolesc Psychiatry* 32:350–353

Steingard RJ, Goldberg M, Lee D, DeMaso DR (1994), Adjunctive clonazepam treatment of tic symptoms in children with comorbid tic disorders and ADHD. *J Am Acad Child Adolesc Psychiatry* 33:394–399

Sverd J, Gadow KD, Paolicelli LM (1989), Methylphenidate treatment of attention-deficit hyperactivity disorder in boys with Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry* 28:574–579

Swanson JM, Flockhart D, Udrea D, Cantwell D, Connor D, Williams L (1995), Clonidine in the treatment of ADHD: questions about safety and efficacy (letter). *J Child Adolesc Psychopharmacol* 5:301–304

Tourette Syndrome Classification Study Group (1993), Definitions and classification of tic disorders. *Arch Neurol* 50:1013–1016

Wechsler D (1974), *Manual for the Wechsler Intelligence Scale for Children-Revised.* New York: Psychological Corporation

Werry JS, Sprague RL, Cohen MN (1975), Conners' Teacher Rating Scale for use in drug studies with children: an empirical study. *J Abnorm Child Psychol* 3:217–229

Wilens TE, Spencer T, Biederman J, Wozniak J, Connor D (1995), Combined pharmacotherapy: an emerging trend in pediatric psychopharmacology. *J Am Acad Child Adolesc Psychiatry* 34:110–112

Woodcock RW, Johnson BB (1977), *Woodcock-Johnson Psychoeducational Battery.* Allen, TX: DLM Teaching Resources